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The pattern of bone marrow involvement among chronic lymphocytic leukemia patients and its impact on the disease outcome in Kurdistan Region of Iraq

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Abstract:

OBJECTIVES: There are the variable degrees of bone marrow (BM) infiltration patterns in chronic lymphocytic leukemia (CLL). Four BM patterns: Interstitial, nodular, mixed, and diffuse patterns were identified. The aim of this study is to assess the effects of BM infiltration patterns on the disease outcome among CLL patients in Kurdistan Region of Iraq.

METHODS: This study is a cross-sectional, descriptive, retrospective involved 106 patients with CLL disease. The data are collected in the Kurdistan region of Iraq (including Erbil, Sulaymaniyah, and Duhok) cancer centers. Through the period from January 1, 2010 to December 31, 2019. BM histopathology study of all patients was assessed and correlated with the disease outcome.

RESULTS: Fifty-three (50.0%) patients had interstitial BM patterns, 17 (16.0%) had nodular BM pattern, 14 (13.2%) had mixed BM patterns, and 22 (20.8%) had diffuse BM pattern. The results showed that patients with interstitial, nodular, and mixed BM patterns had a superior overall survival (OS) and progression-free survival (PFS) rate than diffuse BM pattern. Kaplan–Meier curve illustrates that our CLL patients with interstitial BM patterns had a better mean OS rate (44.0 months) than diffuse BM pattern with a mean of (23.2 months). As well as for PFS, the mean was (35.7 months) for the interstitial BM patterns and (17.6 months) for diffuse BM pattern.

CONCLUSIONS: We demonstrate that the BM involvement patterns have a prognostic value in our CLL patients and provide more reliable information regarding the clinical outcome.

Keywords:

Bone marrow, chronic lymphocytic leukemia, overall survival, progression-free survival

Introduction

Chronic lymphocytic leukemia (CLL) is an indolent malignancy of B-cells defined by lymphocytosis of peripheral blood (PB) and bone marrow (BM), variable degrees of lymphadenopathy, splenomegaly, and cytopenia. CLL is considered as the prevalent adult leukemia in western counties with of 4.2:1,00,000/year incident rate.[1,2] Approximately its account about 25%–35% of all leukemias in the United

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States.[3] CLL known to be a predominant disease in the old age patients, which has a median age around 70 years at the time of diagnosis.[4]

Most CLL patients are diagnosed by accidental observation of asymptomatic leukocytosis or lymphocytosis, painless lymphadenopathy, or/splenomegaly, and only 20% of patients have a symptomatic illness. Patients may present with anemia and thrombocytopenia associated symptoms, symptomatic lymphadenopathy or splenomegaly (abdominal pain, distention, or early satiety), or constitutional symptoms. On physical examination, they may have rubbery, firm, nontender, symmetrical lymphadenopathy, and palpable spleen or liver enlargement.

The updated guidelines of CLL diagnosis, treatment indication, and assessment of response are recently published by the International Workshop on CLL. This guideline needs at least 5×10^9/L of B-cell count in PB to make a diagnosis of CLL in a patient with already documented immunophenotype of the CLL B-cell population.[5-7]

The gold standard for establishing the CLL diagnosis is by flow cytometry (FC) by a demonstration of mature B-cells with CLL-specific immunophenotype. Which is characteristically express B cell-antigen (CD19+, dim CD20+, and CD23+), as well as low levels of (SmIg), and co-expression of T antigen CD5.[5,8,9]

The clinical staging, Rai and Binet are the cornerstone of the prognosis evaluation and suggest therapy for patients with CLL, although it was introduced 30 years ago. Reliable information on survival probability is given by Rai and Binet staging systems. Stage (Rai 0, Binet A) patients typically have low-risk disease, stage (Rai I, II; Binet B) considered as an intermediate-risk disease, and stage (Rai III, IV; Binet C) considered as a high-risk disease.[10,11]

There are a variable degree of BM infiltration patterns: - interstitial (good prognosis) 30%, mixed (nodular + interstitial) 25%, nodular 10%, and diffuse 25% (poor prognosis). The nodular and interstitial patterns are predominating in the early clinical stage, while the diffuse pattern predominates in the advanced stage. In general, the BM examination is not vital in CLL diagnosis, but it' is recommended before starting therapy and in complex cases to give us valuable information about the causes of cytopenias.[2,10,12]

BM study, even when not essential for diagnosis, is still beneficial for prognosis based on the diffuse and nondiffuse infiltration pattern. Several studies document the prognostic importance of the CLL BM infiltration pattern, with shorter survival and poor prognosis are associated with diffuse BM involvement.[13]

The main aim of this study to assess the effects of BM infiltration patterns on the disease outcome among CLL patients in Kurdistan Region of Iraq.

Methods

This study is a cross-sectional, descriptive, retrospective to correlate BM involvement with the overall survival (OS) and mortality rate of 106 CLL patients. The data were collected in the Kurdistan region of Iraq including (Erbil, Sulaymaniyah, and Duhok) cancer centers. Through the period from January 1, 2010m to December 31, 2020.

The data have been collected on case sheets and formulated as variables for the SPSS statistical analysis. The inclusion criteria are all age group CLL patients who were diagnosed at or referred to Regional Hematology-Oncology Centers in Kurdistan regions. While the patients without initial BM biopsy are excluded from this study.

A sample of 250 CLL patients was chosen after qualifying the inclusion and exclusion criteria just 106 patients included. All the patients in this study have complete blood picture, BM exam, biochemistry investigation such as liver function tests, renal function tests, lactic dehydrogenase, most of them they have an abdominal ultrasound and FC.

The questionnaire developed and included the required data as age, gender, residence, Eastern Cooperative Oncology Group (ECOG) performance state, BM infiltration patterns (interstitial, nodular, mixed, and diffuse). Moreover, we assess the OS (in months) and mortality rate according to the disease outcome.

All the laboratory tools needed to diagnose the disease were performed at Kurdistan Region Cancer Center Laboratories.

As part of the initial diagnostic process, needle biopsies and aspirates were taken from the posterior iliac crest. Biopsies that had been decalcified were fixed in formalin, paraffin embedded, and stained with hematoxylin and osin.

All specimens were reviewed by a one pathologist who had no prior knowledge of the patients' clinical data. There were four different patterns obtained to identify the BM biopsy result as follows:

(a) interstitial pattern (hematopoietic replacement by mature lymphocyte with fat cell and BM structure perseveration), (b) nodular pattern (nodular infiltration which is made by mature lymphocyte, fat cell, and BM structure also is preserved, (c) mixed pattern (it has both

characteristics of the interstitial and nodular patterns), and (d) diffuse (the abnormal lymphocytes fully replace the BM hematopoietic structure).[14-17]

The statistical analysis was conducted using version 27.0 of the SPSS software (IBM Corp., Chicago, Illinois, USA), the data were presented on the charts and tables after the missing values were excluded.

For the results analysis, we used the Chi-square and Fisher's exact test. The Kaplan–Meier curve has been used to test the survival of patients with CLL. If (*P* value) is 0.05 or less, it is regarded as statistically significant.

The study accepted by the Ethics Committee of Kurdistan Board for Medical Specialties and Cancer Centers which are followed the Helsinki Declaration.

Results

The clinical characteristics of 106 patients in our study are shown in Table 1. The mean age was (62.8) with a range of 35–92 years at the time of diagnosis. Fifty-nine of them (55.7%) were in the age group of <65 years and 47 (44.3%) were in the age group of ≥65 years. Sixty-nine (65.1%) patients were males, while male-to-female ratio was 1.8:1. The patients' residence were as follows: Erbil 71 (67%), Sulaymaniyah 17 (16%), and Duhok 18 (17%) [Table 1].

For Rai staging, there were 37 (34.9%) patients who had Stage 0, 43 (40.6%) who had Stage I-II, and 26 (24.5%) who had Stage III-IV. For Binet staging system, 48 (45.3%) patients were in Stage A, 31 (29.2%) were in Stage B, and 27 (25.5%) were in Stage C. The ECOG performance of 0–1 was (82.1%) in the majority of the patients. Eighty-three (78.3%) patients were alive and 23 (21.7%) patients died [Table 1].

According to the BM involvement patterns, 53 (50.0%) patients had interstitial BM patterns, 17 (16.0%) patients had nodular BM pattern, 14 (13.2%) patients had mixed BM pattern, and 22 (20.8%) patients had diffuse BM pattern [Figure 1].

The mean survival of all CLL patients in this study was (38 months), (52.8%) of them had <3 years survival and (47.2%) of them had 3 years survival and more, and the mean for progression-free survival (PFS) was (30.4 months), meanwhile (60.4%) of them had PFS <3 years and (39.6%) of them were 3 years and more [Table 1].

Table 2 shows the comparison of BM involvement patterns in terms of age, gender, Rai stage, Binet stage,

Table 1: The statistical charsteristics of the patients (*n*=106)

	Frequency, *n* (%)
Age group	
<65	59 (55.7)
≥65	47 (44.3)
Gender	
Male	69 (65.1)
Female	37 (34.9)
Government	
Erbil	71 (67.0)
Sulaymaniyah	17 (16.0)
Duhok	18 (17.0)
Bm patterns	
Interstitial	53 (50.0)
Nodular	17 (16.0)
Mixed	14 (13.2)
Diffuse	22 (20.8)
Rai staging	
0	37 (34.9)
1-2	43 (40.6)
3-4	26 (24.5)
Binet staging	
Stage A	48 (45.3)
Stage B	31 (29.2)
Stage C	27 (25.5)
ECOG	
0-1	87 (82.1)
≥2	19 (17.9)
Mortality rate	
Alive	83 (78.3)
Dead	23 (21.7)
OS (year), mean±SD	38±26.6
<3	56 (52.8)
≥3	50 (47.2)
PFS (years), mean±SD	30.4±26.1
<3	64 (60.4)
≥3	42 (39.6)

BM=Bone marrow, ECOG=Eastern Co-operative Oncology Group, OS=Overall survival, PFS=Progression-free survival, SD=Standard deviation

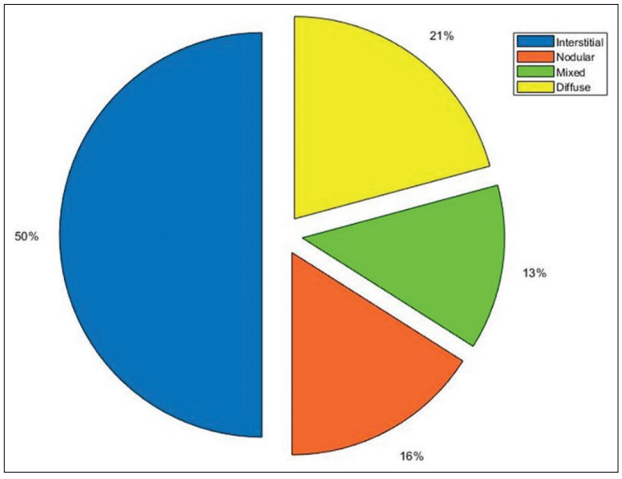

Figure 1: Four bone marrow infiltration patterns in chronic lymphocytic leukemia patients in the kurdistan region of Iraq (*N* = 106)

and mortality rate. A significant correlation found that the patients with diffuse BM pattern had advanced age ($P = 0.01$), higher mortality rate (66.2%) ($P < 0.001$), and also had advance Rai and Binet staging ($P < 0.001$).

No significant association was observed between the BM patterns and patient gender ($P < 0.7$)

A significant correlation was found between BM pattern with OS and PFS by using the Chi-square test in our CLL patients. The results showed that patients with interstitial, nodular, and mixed BM patterns had a superior OS and PFS survival rate than diffuse BM pattern [Table 3].

For interstitial BM pattern, the survival rate of <3 years was 39.0%, and for those ≥3 years was 62.0% ($P < 0.04$). Moreover, the diffuse pattern had an inferior survival rate with <3 years was 30.4%, and ≥3 years survival probability of 10.0%, respectively ($P < 0.04$).

The PFS <3 years was 40.6% and PFS ≥3 years was 64.3% among interstitial BM patterns ($P < 0.017$), while the PFS <3 years was 29.7% and PFS ≥3 years was 7.1% among the diffuse BM pattern ($P < 0.017$) [Table 3].

Kaplan–Meier curve illustrates that our CLL patients with interstitial BM patterns had a better mean OS rate (44.0 months) than diffuse BM pattern with a mean of (23.2 months). As well as for PFS, the mean was (35.7 months) for the interstitial BM patterns and (17.6 months) for diffuse BM pattern, as shown in Figures 2 and 3.

Discussion

To the best of our knowledge, there was no study has been published in the Kurdistan region of Iraq on the impacts of BM involvement patterns on the disease outcome in CLL patients.

Although BM study is not essential for the diagnosis and not performed routinely, they still can determine practical and useful information about the CLL disease, especially about the causes of cytopenia and the treatment response.[18,19]

It is known that the CLL patients had a lower survival rate with diffuse BM patterns than others with the nondiffuse BM patterns as well as it is associated with a prognostic significance.[16] With the agreement to other

Table 2: The comparative characteristics with bone marrow patterns (*n*=106)

	Interstitial, *n* (%)	Nodular, *n* (%)	Mixed, *n* (%)	Diffuse, *n* (%)	Total, *n* (%)	*P*
Age (years)						
<65	35 (59.3)	12 (20.3)	4 (6.8)	8 (13.6)	59 (100.0)	0.01* (S)
≥65	18 (38.3)	5 (10.6)	10 (21.3)	14 (29.8)	47 (100.0)	
Gender						
Male	37 (53.6)	11 (15.9)	8 (11.6)	13 (18.8)	69 (100.0)	0.7* (NS)
Female	16 (43.2)	6 (16.2)	6 (16.2)	9 (24.3)	37 (100.0)	
Rai staging						
0	27 (73.0)	4 (10.8)	4 (10.8)	2 (5.4)	37 (100.0)	<0.001** (S)
I–II	23 (53.5)	12 (27.9)	5 (11.6)	3 (7.0)	43 (100.0)	
III–IV	3 (11.5)	1 (3.8)	5 (19.2)	17 (65.4)	26 (100.0)	
Binet staging						
A	34 (70.8)	8 (16.7)	4 (8.3)	2 (4.2)	48 (100.0)	<0.001** (S)
B	16 (51.6)	7 (22.6)	5 (16.1)	3 (9.7)	31 (100.0)	
C	3 (11.1)	2 (7.4)	5 (18.5)	17 (63.0)	27 (100.0)	
Mortality rate						
Dead	5 (21.7)	1 (4.3)	2 (8.7)	15 (65.2)	23 (100.0)	<0.001** (S)
Alive	48 (57.8)	16 (19.3)	12 (14.5)	7 (8.4)	83 (100.0)	
Total	53 (50.0)	17 (16.0)	14 (13.2)	22 (20.8)	106 (100.0)	

*Chi-square test, **Fisher's exact test. S=Significant, NS=Nonsignificant

Table 3: The bone marrow patterns in relation to overall survival and progression-free survival (*n*=106)

BM pattern	OS			PFS			Total, *n* (%)
	<3 years, *n* (%)	≥3 years, *n* (%)	*P*	<3 years, *n* (%)	≥3 years, *n* (%)	*P*	
Interstitial	22 (39.0)	31 (62.0)	0.04 (S)*	26 (40.6)	27 (64.3)	0.017 (S)*	53 (50.0)
Nodular	9 (16.1)	8 (16.0)		9 (14.1)	8 (19.0)		17 (16.0)
Mixed	8 (14.3)	6 (12.0)		10 (15.6)	4 (9.5)		14 (13.2)
Diffuse	17 (30.4)	5 (10.0)		19 (29.7)	3 (7.1)		22 (20.8)
Total, *n* (%)							106 (100)

*Chi-square test. OS=Overall survival, PFS=Progression-free survival, S=Significant, BM=Bone marrow

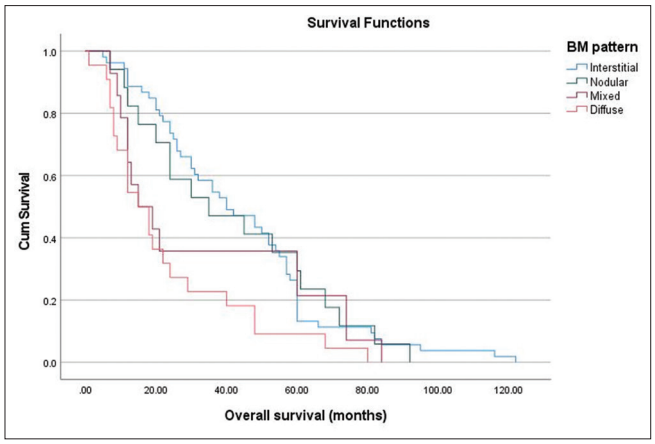

Figure 2: Kaplan–Meier curves showing the overall survival in relation to bone marrow infiltration patterns among chronic lymphocytic leukemia patients in the Kurdistan region of Iraq (*N* = 106)

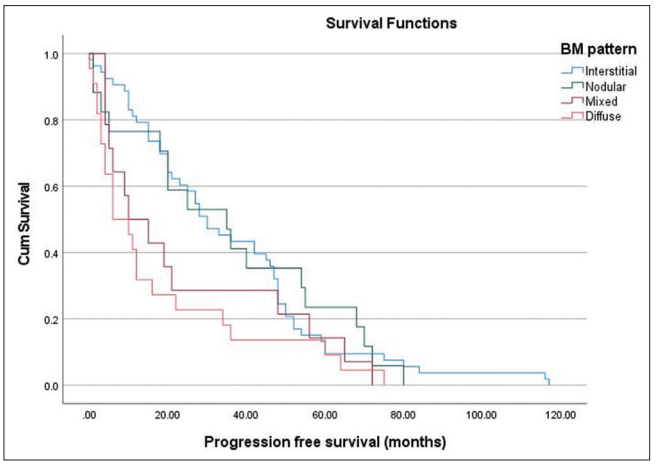

Figure 3: Kaplan-Meier curves showing the Progression-free survival (PFS) in relation to bone marrow infiltration patterns among chronic lymphocytic leukemia patients in the Kurdistan region of Iraq (*N* = 106)

research, this risk is substantially increased in patients with diffuse BM patterns.[20-23]

The involvement of BM has become a matter of interest and conflict for more than two decades as a prognostic predictor. No research doubts the association between the BM involvement pattern and clinical staging, all of which report a clustering of nondiffuse BM patterns in the early stages while in the later stages it reports a diffuse pattern.[20,23-29]

In this regard, it is of importance that in the current study there is a highly correlated result obtained between BM histological patterns and clinical staging systems in CLL patients. When comparing with the other BM patterns, we noticed that the interstitial BM pattern was more prevalent in the early stages, there were 27 of 53 patients in Stage 0 had an interstitial BM pattern according to Rai staging system while there are only 3 of 53 patients in Stages III-IV had an interstitial BM pattern ($P < 0.001$). This finding coincides with the results of Zengin *et al*. study in Turkey and Jahic *et al.* study in Bosnia, also we demonstrate a similar correlation with the Binet staging system.[17,30]

In the current study, we identified a correlation between BM patterns and PFS, as we noticed there is an obvious shortening of the PFS in diffuse BM pattern. Diffuse BM pattern had a shorter PFS than the other BM patterns with a mean of PFS (17.6 months). These findings are similar to other studies done, as it found to be consistent with the results that were reported in Mauro *et al*.[27] study in Italy, confirmed the unfavorable effect of diffuse BM pattern on PFS probability with a mean PFS (20 months), also this finding is close to results of Geisler *et al*.[20] study in Denmark which they confirmed the shortening of PFS according to the four BM patterns.

In our study as predicted, the patients who had a diffuse BM pattern have an inferior survival rate than those with nondiffuse BM patterns (interstitial, nodular, and mixed patterns), the mean survival probability for diffuse BM pattern was 23.2 months as compared to 44.0 months in interstitial BM patterns ($P = 0.004$), where the same results obtained in Mauro *et al*.,[27] they noticed the shorter OS probability in the patients with diffuse BM pattern ($P = 0.01$). As well as in Geisler *et al*., they found the survival probability significantly correlated to diffuse BM pattern.[25] Rozman *et al*. study in Spain found a higher survival rate of interstitial than of mixed cases.[15]

We also obtained the mortality rate was higher in CLL patients who had a diffuse BM pattern than in patients with other types of BM patterns (interstitial, nodular, and mixed patterns), it was 65.2% ($P < 0.001$). These results are also observed by Pangalis *et al.* study Greece, they found the death rate was more frequent in diffuse BM pattern in comparison to other BM patterns.[13] Although in Geisler *et al*. which they found that the diffuse BM pattern had a fourfold higher mortality rate in comparison to nondiffuse patterns in early stages.[25]

In the current study, there is no correlation between the gender of CLL patients in relation to BM patterns, since the ratios of both genders with diffuse or nondiffuse BM patterns are essentially similar ($P = 0.7$). However, we found a strong association in BM patterns in relation to the age of the patients, we noticed that the diffuse BM pattern usually presents in advanced age ($P = 0.01$), these observations are in conflict with what they obtained by Jahic *et al.*, although we have the same mean age (62.8 years) of the CLL patients in both studies.[30] This conflict may be due to the difference in the total patient's number involved in both studies, and hence, further analysis is needed to confirm the results.

Conclusions

In conclusion, the results in our study demonstrate that BM infiltration patterns in CLL disease have higher OS and PFS in a proportion of patients. These data support BM infiltration patterns that are founded as a predictor factor for survival probability in CLL patients, as disease progression prediction is highly critical in CLL disease. Finally, we recommend that further researches are needed in Iraq to concreate the results of this study as there are many patients excluded because they did not have BM examination study.

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Conflicts of interest
There are no conflicts of interest.

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